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EXAMINER
SANDALS, WILLIAM O

ART UNIT	PAPER NUMBER
1636	12

DATE MAILED: 07/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/817,003	Sabatini
Examiner	**Art Unit**
William Sandals	1636

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 18, 2002*

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *38-159* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *38-159* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Mar 18, 2002* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examine

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *7, 12*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Claims

1. Claims 38-159 are pending. Claims 1-37 have been cancelled. New claims 38-159 have been added by amendment in Paper No. 11, filed March 18, 2002.

2. In view of the cancellation of claims 1-37, all previous rejections of the claims are moot, and likewise, the arguments regarding the rejections are moot.

3. New grounds of rejection are presented below.

Priority

4. The priority claim entered in Paper No. 8, filed January 17, 2002 has met all the requirements of 37 CFR 1.78, and priority has been established accordingly.

Drawings

5. The drawings as submitted on March 18, 2002, have been approved by the draftsman.

Claim Objections

6. Claim 80 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the

claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 80 depends from claim 38.

Claim 80 recites that the "affixed plurality of nucleic acid molecules form an array of nucleic acid molecules and wherein said cells into which the nucleic acid molecules are introduced form an array of cells comprising the nucleic acid molecules.

Claim 38 recites at lines 13-17 "the affixed plurality of nucleic acid molecules forms an array comprising at least 10 different discrete sequences and whereby the nucleic acid molecules are introduced into the eukaryotic cells in the location in which the nucleic acid molecules were deposited, thereby forming an array of cells comprising the nucleic acid molecules."

Claim 38 specifies that the nucleic acid molecules are in an array, and that the cells are in an array. Therefore, the limitations of claim 80 are duplicative and redundant, and fail to further limit claim 38.

7. Claims 135 and 136 are objected to because of the following informalities: claims 135 and 136 recite that the locations are 200-500 mm and 400 mm apart, respectively. The designation "mm" should be changed to "μm". Appropriate correction is required.

Claim Rejections - 35 USC § 112

8.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 81 96, 103, 105 and 159 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 81 is drawn to an array produced by the method of claim 38. Claim 38 recites an array of nucleic acid molecules and an array of cells. The array of claim 81 may be either of these arrays, and since claim 81 is not specific about which one of the arrays is meant to be claimed, the claim 81 is therefore vague and indefinite.

11. Claim 96 recites "a library comprising coding sequences that are expressed as a portion of a chimeric protein, the chimeric protein optionally comprising an unstructured polypeptide linker region between one or more of the portions derived from different proteins." One of ordinary skill in the art would not know how to interpret the metes and bounds of this limitation. A derivation of a protein may be closely patterned after the subject protein or may be very loosely patterned after the subject protein, such that it may bear no resemblance or form recognizable as the subject protein which may be chemically and/or biologically totally unrelated in function or form to the subject protein.

12. Claim 96 recites the limitation "the portions derived from different proteins" in lines 4-5. There is insufficient antecedent basis for this limitation in the claim.

13. Claim 103 is drawn to an array produced by the method of claim 102 which ultimately depends from claim 38. Claim 38 recites an array of nucleic acid molecules and an array of cells.

The array of claim 103 may be either of these arrays, and since claim 103 is not specific about which one of the arrays is meant to be claimed, the claim 103 is therefore vague and indefinite.

14. Claims 105 and 159 recite the term "molecules having additional functions". "Molecules having additional functions" are not defined in the specification or claims. Without proper guidance as to the meaning of the term, one of ordinary skill in the art would not know the metes and bounds of the claim.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 38, 46, 47, 49, 51, 52, 57-59, 74-81, 83-86, 98-100, 104-109, 111, 116-123, 125-128, 131-137, 139-142, 154, 155, 158 and 159 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,576,752 (Manoharan et al.) in view of US 6,368,838 (Singhvi et al.).

The claims are drawn to a method of introducing nucleic acid molecules into a eukaryotic cell, a method of affixing a nucleic acid to a surface to produce an array of nucleic acid molecules in discrete defined locations, an array of cells, and an array of nucleic acids. The

nucleic acid is affixed to the surface in a solution comprising gelatin, and then dried. The eukaryotic cells are layered onto the surface and the nucleic acids enter the eukaryotic cells. The array comprises at least 10 discrete sequences. The array provides a density of at least 10^2 - 10^6 features per cm^2. The surface may be glass, polystyrene or plastic, which may be a slide. The eukaryotic cells may be mammalian cells. The nucleic acid may be DNA or RNA. The nucleic acid molecule may inhibit a function in the cell. The array may comprise 100, 1,000 or 10,000 discrete defined locations. Each location may be 100-200 μm in diameter and may be 200-500 (or 400) μm apart. The cells may be from various tissues. The cells may be engineered to express one or more recombinant genes, have a loss of function/gain of function phenotype, or express a cell surface receptor. The nucleic acid may be from 200 bases to 10Kb in size. The surface may be a microsphere or fiber optic system. The nucleic acid may be transferred to a second surface.

Manoharan et al. teach at column 5, lines 26-32, column 7, lines 28-50, column 14, lines 5-48 and examples 38 and 39, an array of a nucleic acid molecules and a method of making the array. Manoharan et al. teach the affixing of nucleic acids to a surface in an array. Eukaryotic cells are layered onto the surface and the nucleic acid enters the cells. The nucleic acid and inhibits the function of a gene. The nucleic acid is an antisense oligonucleotide in an array of fifty different sequences (see example 38). The nucleic acid is DNA or RNA. The cell may have been engineered to express a recombinant gene (HDAC). The solid support may be glass or plastic (see column 13, lines 50-57)

Manoharan et al. do not teach the dimensions of the features of the arrays or the density of features on the surface, nor the cell types which may be used in the method, nor that gelatin is comprised in the solution with the nucleic acids applied to the surface.

Singhvi et al. teach at the abstract, column 3, lines 49-59, column 8, line 19 - column 9, line 61, column 10, line 60-column 11, line 19, column 12, line 41-column 13, line 11, column 17, lines 13-43, column 18, lines 1-23, column 20, line 61-column 21, line 6, an array of nucleic acids, an array of cells, and methods of making the arrays. Singhvi et al. teach at column 3, lines 10-59 that the dimensions of the discrete locations of the array on the surface can be as small as 0.2 μm, and that they may be as large as 2,500 μm^2 . (Simple mathematical calculations indicate that the array can provide a density of at least 10^2 - 10^6 features per cm^2.) The surface may be glass, plastic or polystyrene. Singhvi et al. teach multiple cell types which may be bound (see column 15, lines 44-47 and column 19, lines 1-8). Singhvi et al. teach extracellular matrix proteins fibronectin, collagen and laminin and serum albumin as well as polysaccharides, simple and complex carbohydrates and sugars comprising the materials used in binding the nucleic acids and cells to the surface (see column 9). Singhvi et al. teach that different cells have different physical sizes and dimensions, and that the size and shape of the array may be varied accordingly. The extracellular proteins and polysaccharides cited by Singhvi et al. are components of gelatin.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to modify an array of nucleic acids immobilized on a surface, where the

nucleic acids enter cells layered onto the surface, and where the nucleic acids inhibit the expression of a gene in the cell as taught by Manoharan et al. with the arrays of nucleic acids and cells of Singhvi et al. for the expected benefit of modifying the array in multiple aspects to best suit the physical requirements of transfer of nucleic acids to the cells of the method. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Manoharan et. al. who demonstrate an array of nucleic acids and a method of transfer of the nucleic acid into a cell and Singhvi et. al. who demonstrate a method of making an array of nucleic acids and an array of cells.

17. Claims 38-72, 74-86, 98-100, 104-137, 139-142, 154, 158 and 159 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,576,752 (Manoharan et al.) in view of US 6,368,838 (Singhvi et al.) as applied to claims 38, 46, 47, 49, 51, 52, 57-59, 74-81, 83-86, 98-100, 104-109, 111, 116-123, 125-128, 131-137, 139-142, 154, 155, 158 and 159 above, and further in view of US 5,811,274 (Palsson et al.).

The claims are drawn to the invention as described above and where the nucleic acid mixture comprises a lipid transfection reagent and a sugar, and where the surface may be coated with polylysine.

Manoharan et al. and Singhvi et al. teach the invention as described above.

Manoharan et al. and Singhvi et al. do not teach that the nucleic acid mixture comprises a lipid transfection reagent and a sugar, and where the surface may be coated with polylysine.

Palsson et al. teach the transfer of a nucleic acid into a cell on a surface at the abstract and summary. The surface may be coated with gelatin or polylysine (see column 5, lines 50-59). The surface may be glass or plastic (see column 6, lines 1-26). The nucleic acids may be in a mixture comprising a lipid transfection reagent, which may also comprise a sugar (see column 8, lines 28-43). Palsson et al. teach at the summary, that the method of transfer of nucleic acid into a cell on a surface provides increased transfection efficiency.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to modify an array of nucleic acids immobilized on a surface, where the nucleic acids enter cells layered onto the surface, and where the nucleic acids inhibit the expression of a gene in the cell using the arrays of nucleic acids and cells as taught by Manoharan et al. and Singhvi et al. with the method of transfer of nucleic acids into cells on a surface as taught by Palsson et al. One of ordinary skill in the art would have been motivated to combine the teachings of Manoharan et al., Singhvi et al. and Palsson et al. for the expected benefit of improving the efficiency of transfer of nucleic acids to the cells. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Manoharan et. al. who demonstrate an array of nucleic acids and a method of transfer of the nucleic acid into a cell, Singhvi et. al. who demonstrate a

method of making an array of nucleic acids and an array of cells and Palsson et al. who demonstrate increased efficiency of transfer of nucleic acids into a cell on a surface.

18. Claims 38-72, 74-100, 104-137 and 139-159 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,576,752 (Manoharan et al.) in view of US 6,368,838 (Singhvi et al.) and further in view of US 5,811,274 (Palsson et al.) as applied to claims 38-72, 74-86, 98-100, 104-137, 139-142, 154, 158 and 159 above, and further in view of US 5,753,432 (Gudkov et al.).

The claims are drawn to the invention as described above and where the nucleic acid comprises a library.

Manoharan et al., Singhvi et al. and Palsson et al. teach the invention as described above.

Manoharan et al., Singhvi et al. and Palsson et al. do not teach that the nucleic acid comprises a library.

Gudkov et al. teach at column 6, line 23 to column 9, line 24, the creation of a library of nucleic acids which are transferred into cells for expression of the nucleic acid. The nucleic acid may be an antisense nucleic acid which inhibits expression of a gene in the cells. The expression of the library of nucleic acids confers a transformed phenotype upon the cell which receives the nucleic acid (see the summary at the top of column 4).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to modify an array of nucleic acids immobilized on a surface, where the nucleic acids enter cells layered onto the surface, where the nucleic acids inhibit the expression

of a gene in the cell, where the nucleic acids are in an array and are transferred into cells as taught by Manoharan et al., Singhvi et al. and Palsson et al. with the library of nucleic acids transferred into cells as taught by Gudkov et al. One of ordinary skill in the art would have been motivated to combine the teachings of Manoharan et al., Singhvi et al., Palsson et al. and Gudkov et al. for the expected benefit of conferring a transformed phenotype due to the transfer of nucleic acids to the cells in the method. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Manoharan et. al. who demonstrate an array of nucleic acids and a method of transfer of the nucleic acid into a cell, Singhvi et. al. who demonstrate a method of making an array of nucleic acids and an array of cells, Palsson et al. who demonstrate increased efficiency of transfer of nucleic acids into a cell on a surface and Gudkov et al. who demonstrate the transfer of a library of nucleic acids into cells to produce a transformed phenotype in the cells.

19. Claims 38-159 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,576,752 (Manoharan et al.) in view of US 6,368,838 (Singhvi et al.) and further in view of US 5,811,274 (Palsson et al.) and US 5,753,432 (Gudkov et al.) as applied to claims 38-72, 74-100, 104-137 and 139-159 above, and further in view of US 5,976.807 (Horlick et al.).

The claims are drawn to the invention as described above and where two or more nucleic acids are transferred into the cells.

Manoharan et al., Singhvi et al., Palsson et al. and Gudkov et al. teach the invention as described above.

Manoharan et al., Singhvi et al., Palsson et al. and Gudkov et al. do not teach two or more nucleic acids are transferred into the cells.

Horlick et al. teach at the column 1, lines 9-25 and at the summary the desirability of transferring more than one nucleic acid into a cell for producing the desired expression of the nucleic acid, thereby producing the desired [phenotypic] effect.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to modify an array of nucleic acids immobilized on a surface, where the nucleic acids enter cells layered onto the surface. The nucleic acids produce a phenotypic effect by the expression of a gene in the cell. The nucleic acids are in an array and are transferred into cells as taught by Manoharan et al., Singhvi et al., Palsson et al. and Gudkov et al. with the at least two nucleic acids which are transferred into cells as taught by Horlick et al. One of ordinary skill in the art would have been motivated to combine the teachings of Manoharan et al., Singhvi et al., Palsson et al., Gudkov et al. and Horlick et al. for the expected benefit of producing the desired effect (a transformed phenotype) due to the transfer of multiple nucleic acids to the cells. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Manoharan et. al. who demonstrate an array of nucleic acids and a method of transfer of the nucleic acid into a cell, Singhvi et. al. who demonstrate a method of making an array of nucleic acids and an array of

cells, Palsson et al. who demonstrate increased efficiency of transfer of nucleic acids into a cell on a surface, Gudkov et al. who demonstrate the transfer of a library of nucleic acids into cells to produce a transformed phenotype in the cells and Horlick et al. who demonstrate the transfer of multiple nucleic acids into cells to insure the desired expression and phenotype in the recipient cells.

Conclusion

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of

such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Thursday from 8:30 AM to 7:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Tech Center customer service center at telephone number (703) 308-0198.

William Sandals, Ph.D.

Examiner

June 25, 2003

JAMES KETTER
PRIMARY EXAMINER